

a brain tissue sample. Zhao purified the plasmids and grided them onto a nylon membrane filter using a robot. Then, Zhao constructed probes on the filter from purified poly(A)+ RNA, again from brain tissue. Zhao then hybridized tissue samples with the filter. Then, using a Bioimaging Analyzer and an automatic quantification program, Zhao analyzed the amount of radioactivity existing at each of the probes and performed a data analysis as illustrated by a series of graphs in Fig. 3, page 211. Finally, Zhao performed sequence analysis for clones of interest. Thus, at the time of producing the graph, Zhao did not know the sequence or other characteristics of the cDNA sequences used as probes. It is only after he has displayed expression levels in the graph that he proposes to conduct experiments to determine the sequence of particular probes.

Seilhamer describes a relational database which stores sequencing data in a manner that facilitates cataloguing and searching of protein sequences. Database access is made according to protein function hierarchies. The hierarchical structure is designed to allow cataloguing and searching of sequences based on a protein's biological function or molecular function.

The Zhao method does not disclose providing a display of identification information about expressed sequences responsive to a user's selection of a displayed mark. Rather, Zhao describes a technique for large-scale analysis to detect "the expression of thousands of cDNAs." It is respectfully noted that the combined references do not suggest the method of data retrieval of the present invention.

Zhao is directed to a technique for large-scale quantitative analysis of gene expression. The Zhao technique does not suggest the need to receive user input indicating a particular mark in order to provide the user with information about the gene associated with the mark, for the simple reason that a researcher employing Zhao does not know beforehand the sequence of interest. There is no purpose in providing a user with information retrieval capability in the Zhao technique because the method is performed using cDNA probes of unknown sequence for which there is no *a priori* information available to display. Zhao is completely silent as to the need for any kind information retrieval method.

Seilhamer's hierarchically structured database does not suggest the graphical technique of the present invention. As described beginning at column 19, line 18, the user traverses a hierarchy of menus in order to access information relating to protein function.

By contrast, the present invention provides a user interface for visualizing expression sequence information. Methods, systems and computer programs of the present invention can provide the user with useful information for visualizing the analysis of expression sequences. For example, the present invention provides for display of identification information, such as a GenBank accession number. Further, in some embodiments, the user can encircle multiple marks and obtain a list of information for all genes corresponding to the selected marks. Yet further, embodiments of the present invention can provide non-visual indications of expression level, such as tactile sensations, through a special mouse or pointing device, aural (sound) indications, and the like. Still further, some embodiments of the present invention can obtain information about genes using internet based resources, such as web pages and the like. In sum, the present invention provides significant advances over the state of the art in tools for working with expression sequence analysis.

Seilhamer describes a relational database technique for storing and retrieving gene expression-related data. The technique provides a mechanism for automatically grouping new sequences into protein function hierarchies. Ultimately, the biomolecular sequences stored in databases are contain both descriptive information and category information from a relevant hierarchy or hierarchies. The database contains records pertaining to a plurality of biomolecular sequences. The biomolecular sequences are grouped into a first hierarchy of protein function categories, the protein function categories specifying biological functions of proteins corresponding to the biomolecular sequences and the first hierarchy. The hierarchy includes a first set of protein function categories specifying biological functions at a cellular level, and a second set of protein function categories specifying biological functions at a level above the cellular level. The technique provides a user interface allowing a user to selectively view information regarding the plurality of biomolecular sequences as it relates to the first hierarchy.

In contrast, Applicant's method includes displaying marks relating to expression levels of selected sequences. Input from the user is received, indicating the selection of a

mark. In response to such selection, information about the mark is displayed. Seilhamer does not suggest receiving input which relates to a selected mark on a display. Rather, Seilhamer describes identifying sequences by matching sequences organized hierarchically by protein function. Seilhamer does not suggest providing information on the basis of a selected mark.

Zhao and Seilhamer cannot be fairly combined in a manner which would lead the artisan to arrive at the present invention. The Zhao technique does not lend itself to the notion of providing information for a sequence of interest, since the prior art method begins with unknown probes. Thus, there is no motivation to look to Seilhamer. Moreover, Seilhamer teaches a hierarchical search technique. Therefore, *arguendo*, if Seilhamer is impermissibly combined with Zhao, the present invention still would not be produced. Nothing in the references suggests displaying the identification information about known expressed sequences. For at least these reasons, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,


George B. F. Yee
Reg. No. 37,478

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (650) 326-2400
Fax (650) 326-2422
PA 3048648 v1